PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year*	12 APR 2005
Applicant's or agent's file reference: 12384740	IMPORTANT NOTIFICATION

International Application No.	International Filing Date	Priority Date
PCT/AU2003/001665	12 December 2003	12 December 2002

Applicant: MONASH UNIVERSITY et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001665	International Filing Date *(day/month/year)* 12 December 2003	Priority Date *(day/month/year)* 12 December 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[7] G01N 33/53, 33/574; A61K 39/395; A61P 35/00

Applicant

MONASH UNIVERSITY et al

This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of the report
7 July 2004	11 April 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer DAVID GRIFFITHS Telephone No. (02) 6283

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001665

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001665

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: 59-64

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. 59-64

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 4, 5, 8, 10, 15, 16, 18-29, 39, 41, 48, 50, 52	YES
	Claims 1-3, 6, 7, 9, 11-14, 17, 30-38, 40, 42-47, 49, 51, 53-58	NO
Inventive step (IS)	Claims 18-29	YES
	Claims 1-17, 30-58	NO
Industrial applicability (IA)	Claims 1-58	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

This application relates to the finding that the level of activin βc subunit relative to normal levels is changed in a mammal having a disease condition. Such a condition may be a neoplastic condition. There is disclosed a method for detecting the onset or predisposition to the onset of a condition characterised by an increase or a decrease in the level or bioactivity of activin βc in a mammal. A further aspect of the invention relates to a method of detecting activin β in a sample using first and second antibodies which bind to epitopes of the activin β subunit wherein either the first or second antibody recognises an epitope of an activin βc.

The following documents were raised as relevant by the International Searching Authority:

D1: WO 1998/22492
D2: Mellor SL et al., (2000)
D3: EP 1 174 149
D4: Gold EJ et al., (2003 March)
D5: Mellor SL et al., (2003 Oct)
D6: Vejda S et al., (2002 April)
D7: Thomas TZ et al., (1998)
D8: Risbridger GP et al., (2001)
D9: Dowling CR and Risbridger GP (2000)
D10: Wakui M et al., (2001)
D11: GenexBioscience, Sept 2002

NOVELTY and INVENTIVE STEP: Claims 1-58

Each of the documents D1-D3 and D6-D11 will be discussed below.

Novelty: Claims 1-58

D1: This document anticipates claims 1-3, 7, 9, 11-14, 17, 30-38, 40, 42-47, 49, 51, 53-58 and deprives these claims of novelty.The document teaches that the level of liver activin (activin βc) can be used to diagnose cell growth or differentiation disorders. There are various examples given which are not limited to the liver. On reading this document, a person skilled in the art would consider the measurement of liver activin βc to be useful in the diagnosis of aberrant conditions. The document discloses the use of antibodies to detect amounts of liver activin and also pharmaceutical formulations and methods for regulating cell growth and differentiation.

D2: This document discloses the detection of activin βc subunit protein in human prostate and liver using a monoclonal antibody. The document deprives claims 33-36 of novelty.

D3: This document discusses the roles of activins A, B and AB and the inhibition of activin. The inhibition of activin may be performed using an anti-activin neutralizing antibody. There is however no disclosure of activin βc in this document such that a person skilled in the art would be led to understand that an altered level of activin βc would be indicative of a disease condition.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. There is some ambiguity arising from the term "a predisposition to the onset" of a condition. It is not clear that a person skilled in the art would be able to determine when a "predisposition to the onset" of a condition is indicated from the measurement of the level of activin βc. It has been shown that the level of activin βc is increased following the development of cancer in various tissues. However, the distinction between a modified level of activin βc which can be used to indicate a 'developed' condition and a level of activin βc which can be used to indicate a 'predisposition to the onset' of a condition has not been disclosed.

2. The description on page 22 at line 30 appears to be unclear. It is thought that there should be a reference to a heterodimeric activin AC which is "(β_A-βc)".

3. The description provides support for a modified level of activin βc as an indicator of a cancer or neoplastic condition. There is no support in the description for a link between a modified level of activin βc and any other condition or disease state. As there is such an enormous range of disease states and "conditions", the claims and description appear to be purely speculative in regard to conditions and disease states other than cancer.

4. Claim 16 refers to "activing" AC.

5. It is noted that the International Searching Authority did not search claims 59-64, Claim 63 is directed to a pharmaceutical composition which is defined by its' desired capability, that is, to alter the functionally effective level of activin βc subunit. However, as noted in the ISR, this claim is likely to encompass any number of compounds, many of which may already be known. As the 'agent' itself is not clearly defined, then it is also not possible to provide any opinion on the use of such an agent.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

D6: This document provides evidence for the formation of activin dimers. An activin βc monoclonal antibody is disclosed. Therefore this document deprives claims 33 and 34 of novelty.

D7: This document deprives claim 33 of novelty.

D8: This document discloses the contribution of inhibins and activins to malignant prostate disease. There is a discussion relating to the activin βc subunit as a modulator of activin action. It appears that activin βc may be involved in the regulation of activin A but there is no clear and unmistakable direction towards a link between a modulated level of activin βc and a disease state.

D9: This document involves some discussion on the roles of activin in prostate cancer. It is stated that the activin βc subunit is present in "all grades of cancer in the epithelial cells". It is postulated that the level of activin A may decline through the heterodimerisation of β_A and βc. There is a disclosure of a monoclonal antibody to activin βc. While this document broadly discusses the roles of activin, it is not considered that there is sufficient disclosure which would direct a person skilled in the art to screen for altered levels of activin βc such that a disease state or condition would be cated. This document anticipates the kit of claims 33-34.

D10: This document relates to certain genes which are found to be highly expressed in the early phase of murine graft-versus-host reaction. Activin βc was found to be highly expressed in GVHR mice. GVHR is an immunopathologic process. This document would teach a person skilled in the art that this particular "condition" is linked to an increase in the expression of activin βc. Therefore this document deprives claims 1-3, 6, 11-13, 30, 33, 37, 42, 44, 46-48, 53 and 55 of novelty as GVHR can be regarded as a "condition" which is characterised by modulation of the level of activin βc.

D11: This disclosure deprives claims 33-35 of novelty. An anti-activin beta-c antibody is commercially available. The addition of "reagents" for the detection of antibodies cannot be regarded as a novelty conferring feature as these are widely known and commonly used in the art of immunoassays etc...

Inventive Step: Claims 1-58

Claims 1-3, 6, 7, 9, 11-14, 17, 30-38, 40, 42-47, 49, 51, 53-58 lack an inventive step in light of the comments made above under 'Novelty'.

In addition, claims 4-6, 8, 10, 15, 16, 39, 41, 48, 50 and 52 lack an inventive step in light of D1 as the features of these ms would be obvious to one of skill in this particular art.